



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b>  <b>A61K 9/48</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 92/09274</b>  <b>(43) International Publication Date:</b> 11 June 1992 (11.06.92)
<b>(21) International Application Number:</b> PCT/US91/08998 <b>(22) International Filing Date:</b> 27 November 1991 (27.11.91)  <b>(30) Priority data:</b> 619,133 28 November 1990 (28.11.90) US  <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US 619,133 (CIP) Filed on 28 November 1990 (28.11.90)  <b>(71) Applicant (for all designated States except US):</b> R.P. SCHERER CORPORATION [US/US]; 2075 West Big Beaver Road, Troy, MI 48084 (US).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only) :</b> STROUD, Norman [GB/US]; 217 North Bay Hills Boulevard, Safety Harbor, FL 34695 (US).		<b>(74) Agent:</b> McDONNELL, John, J.; Allegetti & Witcoff, Ltd., Ten South Wacker Drive, Chicago, IL 60606 (US).  <b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), BF (OAPI patent), BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), ML (OAPI patent), MR (OAPI patent), NL (European patent), NO, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US.  <b>Published</b> <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> HIGH AMYLOSE STARCH SUBSTITUTED GELATIN CAPSULES  <b>(57) Abstract</b>  A gelatin capsule sheath in which a portion of the gelatin is replaced with a high amylose content starch to provide a dry capsule sheath having 3-60 % by weight high amylose starch wherein the amylose content of the starch is at least 50 % and preferably 90 % high amylose starch. The capsules of this invention have textured frosted or satin finish which do not stick together, form strong seals, are resistant to changes in shape, and are more economical to manufacture.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MC	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU <sup>+</sup>	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE*	Germany	MC	Monaco	US	United States of America
DK	Denmark				

+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

-1-

## HIGH AMYLOSE STARCH SUBSTITUTED GELATIN CAPSULES

### FIELD OF INVENTION

The present invention relates to gelatin capsules wherein the dry capsule sheath comprises typically 3-60% of a starch having a high amylose content. The capsule sheath also contains other additives such as plasticizers to prevent brittle fracture. The capsule filling may comprise therapeutic agents, dietetic agents and the like.

### BACKGROUND OF THE INVENTION

Soft gelatin capsules comprising principally gelatin, glycerol and water are used for the administration of solids, masses and liquids. They are desirable dosage forms for the administration of many therapeutic substances such as drugs having a bitter taste or are in liquid form. In addition, the gelatin shell wall being readily soluble in the stomach, the contents are more readily absorbed due to the absence of excipients usually present in other oral dosage forms such as tablets and pills. Soft gelatin capsules are particularly suitable for dispensing liquids such as fixed and volatile oils.

The preparation of soft gelatin capsules is described, for example, in Lachman, Theory and Practice of Industrial Pharmacy, Lea & Febiger, Philadelphia, Second Edition, 1986.

U.S. Patent No. 4,804,542 discloses a soft gelatin capsule consisting of a capsule sheath and a capsule filling wherein the capsule sheath consisting of gelatin and a small amount additive in the sheath such as starch, starch derivative, cellulose, cellulose derivative, milk product and so on.

In the usual practice, the empty soft gelatin capsule is filled with the desired material. Thereafter, the empty gelatin capsule is sealed.

### U.S. Patent 3,765,917 (Hijiya)

The Hijiya reference is unambiguously directed to polymer units of 50 glucose units or less (see col. 1, line 23), also see the claims. The material is obtained from fermentive hydrolysis of amylose, see example 3, col. 4, lines

-2-

53-39. The molecular weight for amylose is between about 100,000 and 500,000 daltons.

U.S. Patent 3,865,603 (Szymanski)

5 Szymanski is limited to the use of modified starch, for example, see col. 3, line 2-8. Also see the claims.

U.S. Patent 4,673,438 (Wittwer)

10 The Wittwer patent is directed toward hard capsule and not soft capsules claimed in the present invention. An advantage of the soft capsule in accordance with this invention is the soft capsule has a rough surface which prevents sticking and facilitates printing. Wittwer does not describe the preparation of claim soft capsules and the advantages achieved therein by the present invention.

**SUMMARY OF THE INVENTION**

A new capsule sheath material for making the soft gelatin capsule has been discovered. In this sheath a substantial part of gelatin is replaced with a high amylose starch. The dry capsule contains 3-60% high amylose starch and the high amylose starch contains at least 50% preferably 90% amylose. The soft gelatin capsule comprising this sheath material is manufactured in accordance with known procedures such as that described in U.S. Patents 4,804,542 or 4,744,988.

The soft gelatin capsules prepared in accordance with this invention are characterized as having a textured frosted or satin finish depending on the starch selected. The surface of the capsule in contrast to prior art soft gelatin capsules is rougher thereby preventing the gelatin capsules from sticking especially during storage under humid conditions.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention relates to soft gelatin capsules wherein a substantial part of gelatin is replaced by starch having a high amylose content.

Starch is the most common carbohydrate reserve found in varying amounts in almost all plant members. Starch of commerce, from whatever source it may have been extracted, consists of two or three chemically individual substances all closely related to the sugars distributed throughout the body of the starch granule in different physical states. The important constituents are amylose, amylopectin and amylo-hemicellulose. The first two constituents are present in all starches while the third is found in certain starches such as those derived from graminaceous seeds. Amylose is essentially a linear or partially branched polymer of alpha (1-4) D-glucose, amylopectin is a densely branched, high molecular weight polymer of alpha (1-4) and (1-6) linked glucose units. The molecular weights are  $1 - 5 \times 10^5$  Daltons and  $1 - 50 \times 10^5$  Daltons respectively for amylose and amylopectin. Amylose constitutes the film forming (gel-forming) component of starches.

Starch of high amylose content is indicated as the starch to be incorporated in the capsule sheath of the present invention. The term "high amylose starch" refers to those starches having an amylose content of at least 50% and those having 90% or more is most preferred. "Gelatin" as used

-4-

herein includes those obtained from animal sources as well as modified gelatin such as succinated gelatin. When high amylose starch is incorporated in the capsule sheath, the resulting capsule exhibits a textured frosted or satin finish. This surface is quite advantageous if the capsule is to be coated with an enteric coating and possess very strong seals. Moreover, such a capsule containing a high starch content allows the successful encapsulation of products having an appreciable level of water. Furthermore, such capsules have been shown to be much more resistant to changes in capsule shape than normal gelatin capsules during extended storage. From a cost point of view, starch is much cheaper than gelatin, and a considerable benefit in terms of a cost savings can readily be achieved.

Among the starches having high amylose content are, for example, potato starch, maranta starch or those available commercially under the tradename Amylose PF from Tunnel-Avebe or Hylon VII starches from National Starch.

In accordance with the present invention, there is provided a soft gelatin capsule wherein as high as 85% of the gelatin in the sheath is replaced with a high amylose starch.

Table 1 illustrates typical substitutions of starch for gelatin, in accordance with the present invention, first in the initial formulation composition (A), dry capsule shell composition (B), and capsule shell containing about 6% water (C).

-5-

TABLE 1COMPOSITION BY WEIGHT OF CAPSULE SHELL FORMULATIONS**A. Initial Formulation Composition**

		<u>% Substitution</u>										
5		0	5	10	15	25	35	45	55	65	75	85
	Gelatin	44	41.8	39.6	37.4	33.0	28.6	24.2	19.8	15.4	11.0	6.6
	Starch	0	2.2	4.4	6.6	11.0	15.4	19.8	24.2	28.6	33.0	37.4
	Glycerol	20	_____>									
	Water	36	_____>									

**B. Dry Capsule Composition (Anhydrous Shell)**

		<u>% Substitution</u>										
		0	5	10	15	25	35	45	55	65	75	85
	Gelatin	68.75	65.31	61.87	58.43	51.55	44.67	37.79	30.91	24.03	17.15	10.27
	Starch	0	3.44	6.88	10.32	17.20	24.08	30.96	37.84	44.72	51.60	58.48
15	Glycerol	31.25										

**C. Dry Capsule Composition - Approximately 6% Water**

		<u>% Substitution</u>										
		0	5	10	15	25	35	45	55	65	75	86
20	Gelatin	64.61	61.38	58.15	54.92	48.46	42.0	35.54	29.08	22.62	16.16	9.70
	Starch	0	3.23	6.46	9.69	16.15	22.61	29.07	35.53	41.99	48.45	54.91
	Glycerol	29.37	_____>									
	Water	6.02	_____>									

25 The selected high amylose starch, or a suspension of the starch in water or glycerin, is added to a solution of gelatin, glycerin and water. The resultant mixture is heated and blended until a homogenous mixture is obtained. Soft gelatin capsules are prepared from such a mixture, e.g. by the rotary-die encapsulation process.

**SUBSTITUTE SHEET**

-6-

The soft gelatin capsules thus produced generally has a rough surface depending on the starch selection which will allow them to be packed together without the tendency to stick together as commonly occurs with 100% gelatin capsules.

5 In order to further illustrate the practice of this invention, the following examples are included.

#### EXAMPLE 1

A gelatin solution is prepared by mixing together 31.2 kg of gelatin, 16 kg of glycerol and 36 kg potable water. To this there is added 16.8 kg of Amylose PF having an amylose content of at least 90%. Oblong shaped gelatin capsules are prepared from this mixture in which 35% of the gelatin in the capsule sheath is replaced by starch and the capsule wall has a thickness of about 0.030 inches.

15 The capsules are filled with liquid paraffin and sealed. These capsules rupture and the walls dissolve within 30 minutes in water.

#### EXAMPLE 2

A similar formulation using Hylon VII starch in lieu of Amylose PF wherein the amylose content is 70%. The resulting capsules possess both strong seals and good shapes. The finished (dry) capsules possess a smooth, opaque satin finish. The capsules are filled with liquid paraffin and stored at 40 degrees C. for 4 months. New capsules rupture within 1.6 minutes and the walls dissolve within 6.2 minutes.

#### EXAMPLE 3

25 Similar capsules are prepared as in Example 1 with the exception Hylon V starch having a 50% amylose content is employed.



-7-

**EXAMPLE 4****STARCH-EXTENDED GELATIN FORMULATIONS****Typical Formulations for 85% Substitution of Gelatin are as follows:**

5	<b><u>Initial Composition</u></b>		
	Gelatin	6.6	
	Starch	37.4	
	Glycerol	20.0	
	Water	36.0	
		<hr/>	
		100.00	
10	<b><u>Dry Capsule Composition - Anhydrous</u></b>		
			%
	Gelatin	6.6	10.3
	Starch	37.4	58.4
	Glycerol	20.0	31.3
15		<hr/>	
		64.0	
	<b><u>Dry Capsule Composition - 6% Water in Shell</u></b>		
	Gelatin	6.6	9.69
	Starch	37.4	54.92
20	Glycerol	20.0	29.37
	Water	4.1	6.02
		<hr/>	<hr/>
		68.1	100.00

**I Claim:**

1. A soft gelatin capsule in which the dry capsule sheath comprises 3-60% by weight of a high amylose starch wherein the high amylose starch has at least 50 percent amylose.
2. A soft gelatin capsule according to claim 1 comprising by weight 3 to 60% high amylose starch, 65 to 10% gelatin, and about 31% glycerol.
3. A soft gelatin capsule comprising by weight 3 to 55% high amylose starch, wherein the high amylose starch contains at least 50% amylose, 60 to 10% gelatin, about 30% glycerol and about 6% water.
4. A soft gelatin capsule according to claims 1, 2 or 3 wherein the amylose content of the high amylose starch is at least 50%.
5. A soft gelatin capsule according to claim 4 wherein the amylose content of the high amylose starch is at least 90%.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 91/08998

**I. CLASSIFICATION OF SUBJECT MATTER** (If several classification symbols apply, indicate all)<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/48

**II. FIELDS SEARCHED**Minimum Documentation Searched<sup>7</sup>

Classification System

Classification Symbols

Int.Cl. 5

A61K ; C08L

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>**III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>**

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
Y,P	WO,A,9 014 938 (GOODMANN FIELDER WATTIE AUSTRALIA LTD) 13 December 1990 see page 1, paragraph 1 see page 11, paragraph 2 - page 12, paragraph 2 see page 21 - page 22; example 1 see page 25 - page 26; example 3 ---	1-4
Y	FR,A,2 116 021 (KEN HAYASHIBARA) 7 July 1972 cited in the application see page 1, line 1 - line 3 see page 2, line 8 - line 22 see page 6; example 3 & US,A,3765917 ----- -/-	1-4

<sup>10</sup> Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"d" document member of the same patent family

**IV. CERTIFICATION**

Date of the Actual Completion of the International Search

09 MARCH 1992

Date of Mailing of this International Search Report

15. 04. 92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

BOULOIS D.



III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category <sup>a</sup>	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	US,A,4 804 542 (FISCHER G. ET AL) 14 February 1989 cited in the application see column 2, line 1 - line 10 see column 3, line 59 - column 4, line 3 see column 5; example 1 ---	1-5
A	EP,A,0 118 240 (WARNER-LAMBERT COMPANY) 12 September 1984 cited in the application see page 1, line 3 - line 12 see page 27; example 2 see page 31; example 13 &US,A,4673438 ---	1-5
A	US,A,4 026 986 (CHRISTEN J. D. ET AL) 31 May 1977 See the whole document ---	1-5

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO. US 9108998  
SA 55476**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 09/03/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9014938	13-12-90	None	
FR-A-2116021	07-07-72	DE-A- 2158318	25-05-72
		NL-A- 7116079	26-05-72
		US-A- 3765917	16-10-73
		GB-A- 1333966	17-10-73
US-A-4804542	14-02-89	None	
EP-A-0118240	12-09-84	AU-B- 572119	05-05-88
		AU-A- 2465684	23-08-84
		CA-A- 1238738	28-06-88
		JP-A- 59196335	07-11-84
		US-A- 4673438	16-06-87
		US-A- 4738724	19-04-88
US-A-4026986	31-05-77	None	

EPO FORM P0477

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82